REMARKS

Claims 1-14 and 24-28 are pending in the application. New claims 29-32 have been added. Claims 1-9, 11 and 13 remain rejected, and claims 24-28 stand newly rejected under 35 U.S.C. § 112, first paragraph, as having inadequate written description. Claims 9, 13 and 14 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-9, 11, and 13 remain rejected under 35 U.S.C. § 103(a), as being obvious over Vallee et al., U.S. Patent No. 4,916,073, in view of Olson et al., *Cancer Research* (1994) 54:4576, Milligan et al., *J. Med. Chem.* (1993) 36:1923, Burch, U.S. Patent No. 5,135,917, Anderson et al., U.S. Patent No. 5,442,049, and Artavanis-Tsakonas et al., U.S. Patent No. 5,637,471. Applicants gratefully acknowledge that claims 10 and 12 would be allowable if written in independent form including all of the limitations of the base claim and any intervening claims.

Applicants have amended the claims under consideration to more clearly define and distinctly characterize Applicants' novel invention. Claims 1, 11 and 13 were amended to recite "human" angiogenin, support for which can be found in the specification at least at page 12, lines 1-2 and in Figure 1 which depicts the nucleic acid sequence for human angiogenin. New claims 29-32 were added to recite limitations that were deleted from claim 9. The amendments presented herein contain no new matter.

Applicants respectfully request entry and consideration of the foregoing remarks, which are intended to place this case in condition for allowance.

I. The Specification Provides Adequate Written Description for Claims 1-9, 11, 13, and 24-28

At page 2, paragraph 1 of the instant Office Action, claims 1-9, 11 and 13 remain rejected and claims 24-28 stand newly rejected under 35 U.S.C. § 112, first paragraph, as containing

subject matter which was not described in the specification in such a way as to reasonably convey to those skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that Applicants are only in possession of antisense oligonucleotides targeting the nucleic acid sequence of human angiogenin as set forth in Figure 1 of the specification as filed. The Examiner is of the opinion that further experimentation is required in order for Applicants to determine the sequence of all other polymorphic and allelic variants of angiogenin and furthermore identify antisense oligonucleotides targeting these polymorphic and allelic variants of angiogenin nucleic acid.

Applicants respectfully traverse this rejection. However, without acquiescing to the Examiner's rejections, Applicants have amended claims 1, 11 and 13 to recite a nucleic acid encoding ***human*** angiogenin thereby obviating the Examiner's rejection. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection 1-9, 11, 13, and 24-18 under 35 U.S.C. § 112, first paragraph.

II. Claims 9, 13 and 14 Are Definite

At page 4, paragraph 2 of the instant Office Action, claims 9, 13 and 14 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

The Examiner is of the opinion that claims 9, 13 and 14 recite the broad recitation "O, S, N-alkyl," and the narrower statement of, for example, "SCH_2" and "OCH_3." The Examiner also asserts that these claims recite the term "conjugate," and that every other modification recited in the claims may also be considered a conjugate. The Examiner further asserts that the majority of the modifications recited in the claims may also function to improve the pharmacokinetic or pharmacodynamic properties of oligonucleotides.

In response, Applicants have amended claim 9 to remove certain of these limitations. Newly added claims 29-32 recite the following limitations removed from claim 9: "wherein the modified 2' hydroxyl moiety is selected from the group consisting of OH, SH, SCH_2, OCH_3, F, OCN, OCH_2CH_3, OCH_3CH_3, $OCH_3O(CH_2)_nCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, where n is from 1 to about 10" (recited in claim 29); "wherein the modified 2' hydroxyl moiety is a conjugate" (recited in claim 30); "wherein the modified 2' hydroxyl moiety is a group for improving the pharmacodynamic properties of an oligonucleotide as compared to an unmodified compound" (recited in claim 31); and "wherein the modified 2' hydroxyl moiety is a group for improving the pharmacokinetic properties of an oligonucleotide as compared to an unmodified compound" (recited in claim 32).

The Examiner also asserts that line 3 of claim 9 improperly recites underlining. In response, Applicants submit that claim 9 as now presented does not contain underlining.

The Examiner further asserts that claim 9 recites the term "OCH_6CH_3," which is chemically improper, and suggests amending the term to recite "OCH_2CH_3." Applicants respectfully submit that claim 9 as amended no longer recites this term. Without acquiescing to the Examiner's rejection, Applicants submit that newly added claim 29, which recites limitations which were deleted from claim 9, recites "OCH_2CH_3" instead of "OCH_6CH_3," as suggested by the Examiner.

In view of the above, Applicants respectfully request withdrawal of the rejections of amended claims 9, 13 and 14 under 35 U.S.C. § 112, second paragraph.

III. Claims 1-9, 11 and 13 are Non-Obvious Over Vallee et al. in View of Olson et al., Milligan et al., Burch, Anderson et al., and Artavanis-Tsakonas et al.

At page 5, paragraph 3 of the instant Office Action, claims 1-9, 11, and 13 remain rejected under 35 U.S.C. § 103(a), as being unpatentable over Vallee et al., U.S. Patent No. 4,916,073, in view of Olson et al., *Cancer Research* (1994) 54:4576, Milligan et al., *J. Med. Chem.* (1993) 36:1923, Burch, U.S. Patent No. 5,135,917, Anderson et al., U.S. Patent No. 5,442,049, and Artavanis-Tsakonas et al., U.S. Patent No. 5,637,471. The Examiner is of the opinion that although Milligan et al. does not explicitly teach angiogenin inhibition, Milligan teaches making antisense oligonucleotides if the gene sequence is known. The Examiner asserts that Vallee et al. provides the gene sequence of angiogenin, and that one of ordinary skill in the art would have been motivated to further elucidate the function of angiogenin by inhibiting angiogenin gene expression because Olson et al., which does not explicitly teach antisense oligonucleotides that target angiogenin, does suggest inhibiting angiogenin in order to assess the role of angiogenin in tumor growth. The Examiner concludes that what was known particularly about angiogenin and tumor growth, as taught by the references of Vallee et al. and Olson et al., combined with the teaching of Milligan et al. for employing the antisense art, and the disclosures of Burch, Artavanis-Tsakonas et al., and Anderson for modifying oligonucleotides in general, render the claims obvious. Applicants respectfully traverse the Examiner's rejection.

Vallee et al. teaches the cDNA sequence of the angiogenin gene and the amino acid sequence of the angiogenin protein. Vallee et al. teaches the isolation of the cDNA, and the expression of the angiogenin protein in mammalian tissue culture cells and yeast. Nowhere does Vallee et al. teach or suggest inhibiting the expression of angiogenin using an antisense approach.

Olson et al. teaches that angiogenin is a secreted protein (page 4576, first paragraph and page 4579, top of right column) and that "the antitumor effects exerted by mAb 26-2F (which does not recognize mouse angiogenin) result from the specific extracellular inactivation of tumor-derived human angiogenin" (page 4579, left column, second full paragraph, emphasis added). Thus, Olson teaches nothing of an antisense approach to inhibiting the expression of angiogenin, but instead is directed to inhibiting the angiogenin protein itself which may be present rather than the approach of preventing the generation of angiogenin in the first place.

The Examiner asserts that one of skill in the art would have been motivated to make Applicants' invention because although Milligan et al. does not explicitly teach angiogenin expression, Milligan teaches making antisense oligonucleotides if the gene sequence is known. Applicants respectfully submit that the Examiner's combination of Vallee et al. with the general teachings of Milligan presents the classic obvious-to-try situation which is not the test for obviousness. An obvious-to-try situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*, 916 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990). *See also In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987)(where the PTO failed to establish a prima facie case of obviousness as to the appellant's claim to a method of inhibiting scale formation on and corrosion of metallic parts in cooling water systems by use of compositions containing a certain copolymer, a water soluble zinc compound and a certain acid; "[a]t best, in view of [the disclosures of the prior art], one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents.")

Applicants respectfully submit that Milligan is the type of general teaching that can only lead to an obvious-to-try situation since Milligan is not directed to angiogenin and none of the remaining references cited by the Examiner are sufficient to teach an antisense approach to inhibiting the expression of angiogenin. Milligan only suggests the potential utility of an antisense approach in general when the nucleic acid sequence is known. Milligan only pique's scientific curiosity and may even prompt others to try various antisense approaches, but Milligan itself does not contain a sufficient teaching that an antisense approach to inhibiting the expression of angiogenin will work or that it could work if certain directions were pursued.

In fact, Milligan admits that purported antisense approaches may be operating by non-antisense mechanisms:

> "control of the proliferation of SMCs following injury is complex, and it has been reported previously that simple polyanions such as low-molecular weight heparin also inhibit smooth muscle cell proliferation in animal model systems, again suggesting that the antiproliferative effect may be ***due to a non-antisense mechanism***...[and that a] growing number of target genes which are reported to inhibit SMC proliferation may well be a reflection of the intrinsic activity of ODNs ***rather than the role of the target genes*** in the proliferation of SMCs" (page 1929, paragraph bridging the columns, emphasis added).

Further hurdles to an antisense approach based on Milligan are presented in Applicants' response filed February 2, 2001 and are hereby incorporated by reference. In addition, Milligan maintains a cautionary view with respect to antisense approaches at the introduction paragraph on page 1923:

> In principle, an ODN can be designed to target any single gene within the entire human genome potentially creating therapeutics for any disease in which the causative gene is known. (emphasis added)

After reviewing the state of the art of antisense activity, Milligan et al. maintain their cautionary stance, as evidenced by the conclusion stated on page 1933, second column, bottom paragraph:

> The task for those striving to develop therapeutic antisense molecules is to design the proper ODN derivatives which have the required properties of stability, affinity, permeation, and ultimately, favorable pharmacokinetics. None of the currently available ODN analogues contain all of these properties, and advancement in this field depends upon the development of new, potent antisense agents. (emphasis added)

Milligan therefore only provides speculation of the potential utility of an antisense approach to inhibiting the expression of angiogenin without any evidence of reasonable success of such an approach. Milligan simply invites others to try. Applicant respectfully submits that because Milligan is limited to speculation of the potential of antisense approaches in general, one of ordinary skill in the art would not have been motivated to produce the claimed invention with any reasonable degree of success. Only applicants provide the disclosure to do so. At best, the Examiner's combination of references provides an obvious-to-try situation which is not the standard for obviousness.

In view of the above, Applicants submit that claims 1-9, 11, 13, and 24-28 are patentable over the prior art and respectfully request withdrawal of the rejections of these claims under 35 U.S.C. § 103(a).

IV. Conclusion

Applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

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